Emerging Insights from Animal and Human Studies About the Biomechanics of Concussion

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For a review of current literature on concussion in adults and children: www.iom.edu/concussions
Committee’s Approach

• Reviewed scientific literature and previous reports from the Institute of Medicine and National Research Council

• Reviewed current consensus and position statements relevant to diagnosis and management of concussions

• Held two public workshops

• Focused on youth ages 5 to approximately 21 years

• Took a broad view of sports, defining it as any sort of vigorous physical activity that does not involve motorized vehicles.
Relationship of Concussion to the Spectrum of TBI
Concussion Definition

Concussion is a brain injury induced by biomechanical forces, that may or may not include loss of consciousness, and typically results in a rapid onset of short-lived impairment of neurological function with no abnormalities visible on standard structural neuroimaging studies.

Tolerances are Used to Construct Injury Risk Curves

Mechanical Parameter (i.e. Head Acceleration)

Probability of Injury

- 75% probability of injury
- 50% probability of injury
Thresholds for TBI

• Biomechanical Inputs
  • Acceleration or Velocity
  • Linear or Rotational Movements
  • Centroidal or Noncentroidal Pathways
  • Head Movement Direction
  • Magnitude

• Outputs
  • Symptom severity
  • Persistence of deficits

• Mediating Influences
  • Sex, age, prior exposure, inter-exposure interval
Injury Threshold Development

It Takes The **Whole** Biomechanics Toolbox

- Material Properties
- Animal Models
- Load Estimates
- Human Studies
- Tissue Strain/Stress Thresholds

Computational Model of the Head

Injury Predictions

Prevention and Treatment
Computational Models

- Goal: to create a human surrogate to combine clinical, animal, and in vitro data to estimate injury risk for specific load scenarios

- Include necessary biofidelic properties and anatomy
- Can only predict mechanical responses, not injury
Computational Models

- Checklist for critically evaluating model predictions
  - Geometry/anatomy
    - 2D vs 3D
  - Material properties
    - Age and rate appropriate
  - Loading Conditions
    - Applicable to real-world scenarios
  - Tissue-tissue interactions
    - Brain-CSF-skull
    - Gray/White Matter Interface
  - Purpose of model
    - Injury Prediction or Parametric study
    - Validated?
    - Human data available to estimate injury outcomes?
  - Caution! Garbage In -> Garbage Out
Animal Studies

- **Goal:** propose and test injury mechanisms and therapeutic interventions

- Can measure of injury outcomes AND applied loads
- Acute and secondary injuries
- Range of injury severity and types of TBI (e.g. focal, diffuse)
- Invasive and noninvasive outcomes
- Physiological and neurofunctional outcomes
- Controlled, reproducible loading conditions and injuries

- Challenge – scaling and translating results from animals to humans
Are animal models as good as we think?

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- Why do we need animal models?
- What is a model?
- What makes a \textit{good} model?
- Testing predictability
Rats vs. Porcine Animal Models for TBI

- Rodents have little white matter and small brain size: Difficult to characterize DAI, scale loads

- Pigs have similar gyral pattern and distribution of gray and white matter as humans.

*Buckley, Comp Biochem Physiol, 1986
*Dickerson and Dobbing, Proc Roy Soc Lond, 1967
Large Animal Studies for Diffuse TBI

- Full age spectrum: infant, preadolescent, adult
- Single and repeated head accelerations
- Known injury exposure and history
- Mild to severe brain injury

- Identify
  - Injury thresholds and mechanisms
  - Metabolic and pathophysiology timecourses
  - Inter-injury interval interval vulnerability
  - Therapeutic interventions

Sagittal  Axial  Coronal
Because Human Presentation of TBI is Heterogeneous
Use Multiple Species and Models

Controlled Cortical Impact (CCI)  Rapid Rotation without Impact (RNR)

- focal injury
- cortical contusion
- decreased CBF, metabolic function in underlying ipsilateral hemisphere (rat data)
- ipsilateral necrotic, hypoxic/ischemic damage, tissue swelling
- Somatosensory dysfunction

- diffuse bilateral injury
- widespread white matter damage, subarachnoid hemorrhage and parenchymal tears, bilateral infarcts
- marked decreases in CBF, tissue oxygen content, and mitochondrial function
- sustained cognitive alterations

Margulies et al, Brain Pathology, 2015
Head Rotation Direction Matters
Infant Physiological Response

- Sagittal rotation produced the greatest reductions in cerebral blood flow, beginning ≤10 min post-TBI
- Sagittal rotation produced the worst incidence of apnea and decreases in systemic blood pressure and cerebral perfusion pressure
- Axonal injury is more persistent in sagittal plane injuries than horizontal plane injuries
- Sagittal plane injured animals were more stationary and had less complex motion patterns in the open field tests than horizontal plane injured animals and shams

References:
- Kilbaugh et al, J Neurotr, 2011
- Zhou et al, Jbiomed Optics, 2009
- Weeks et al, J Neurotr, 2014
Using An Integrated Approach To Understand Direction Dependent Acute Axonal Injury

Computational Model

Estimate Shear Modulus for 100% strain, 300 s⁻¹

 Transection Studies

Simulate Animal Studies in 2 ages, 3 directions

DTI Data

Evaluate 27 deformation metrics and determine best Functional Axonal Injury Threshold using ROC

Axonal Pathology

Determine Threshold Performance

Sullivan et al, BMMB, 2014
Tract-oriented Deformation Explains Acute Directional TBI Differences

Angular Velocity

Pop90 Max Principal Strain

Next steps: compare tract-oriented S and SR in quadruped and upright primates

Sullivan et al, 2014
Summary

- Rotational directions resulting in more severe TAI, had larger tract-oriented S, SR and SxSR.
- Tract-oriented S thresholds (6-7%) were similar to isolated CNS tissue thresholds, and lower than death and structural damage thresholds (Bain 2000, Morrison 2006, Cater 2006, Singh 2009).
- Tract-oriented SR threshold 38-40 s⁻¹, similar to others reported for isolated axons (Tang-Schomer 2012).
- S and SxSR thresholds were lower for infants than pre-adolescents.

Sullivan et al, 2014
Outcome Measures

- Pathology and immunohistochemistry to document spatial distribution of neural and vascular injury, repair and regeneration
- Latency to pinch reflex
- Cerebral blood flow
- Blood gases
- Blood pressure and intracranial pressure
- Brain parenchymal oxygen content (Licox)
- Mitochondrial respiration (and tissue microdialysis)
- Serum biomarkers
- Electrophysiology (EEGs)
- Direct ophthalmic exam
- Behavior and cognitive testing
Composite Porcine Disability Score

- **Optimal PDS**
  - Sniffing Toy,
  - Moving Toy
  - $P_{\text{DIAG}}$
  - Lempel-Ziv Complexity
  - Motor Proficiency Score

- Day +1 sensitivity = 87.5%, specificity = 85.7%.
- Day +4 sensitivity = 100%, specificity = 85.7%.

Representative slice from brain with 0.794% volume injury. Circles represent areas of axonal as determined by staining with BAPP.

Ave Injured Volume: 0.86% ± 0.18%
Objective Translational Metrics of Neurofunction
Animals->Humans, Infants->Adults

**Important Features:**
- Nonverbal, summative assessment
- Can be used in awake individuals
- No acclimation or training for the task

- Accelerometer to measure balance and actigraphy (day and night). Similar to FitBit™
- Serum Biomarkers
- Multi-channel EEG Event-related potentials (ERPs)
- Functional Near-infra Red (fNIR) blood oxygen extraction
- MRI, MRS
- PET
Stationary Balance is Altered After TBI

Assessment of Balance:

- iPod accelerometer to assess sway when piglet is standing ‘still’.

- There was significantly increased ML and AP RMS acceleration after a single CCI and significantly increased ML RMS acceleration after a single RNR with no significant change following just sham anesthesia.

1.5-4 hrs post RNR (N=7) and CCI (N=8). Sham anesthesia (N=4)

Jaber et al, Dev Neuropsych 2015
Actigraphy Studies

Actigraphy:

- Tri-axial accelerometers are on the pig’s back while they are in the animal facility both before injury and for days after injury.

- Assess levels of activity in day time and night time (possible sleep disturbances) with pigs in their home environment.

Longitudinal studies extended for 6 days, to capture pre and post TBI
Animals with TBI had larger fractions of inactive periods during the daytime than nighttime, and larger fractions of active time in the night were spent in high activity (e.g. constant walking, intermittent running) than during the day.

These persistent disturbances in rest and activity are similar to those observed in human adults and children after TBI.

Actigraphy is a translational metric, and can be used in both humans and large animals, for the assessment of injury severity, progressions and intervention.

Margulies et al, in review
Metabolic Biomarkers – Serum Amino Acids

ASP: Aspartate or Aspartic Acid
GLU: Glutamate or Glutamic Acid
ASN: Asparagine
SER: Serine
GLN: Glutamine
GLY: Glycine
THR: Threonine
CIT: Citrulline
ARG: Arginine
TAU: Taurine
ALA: Alanine
TYR: Tyrosine
TRYPT: Tryptophan
METH: Methionine
VAL: Valine
PHE: Phenylalanine
IL: Isoleucine
LEU: Leucine
ORN: Ornithine
LYS: Lysine

Significant time effect on ANOVA

Mean +/- SEM
Larger $P_{\text{DIAG}}$ values on Day +4 (more stationary behavior) is correlated with decreases in Valine and Isoleucine at Day +4 from pre-injury.

Significant Correlation
$\rho = -0.87$
$p < 0.01$

Significant Correlation
$\rho = -0.67$
$p < 0.05$
Metabolic Biomarkers – mito-DNA fragments

Kilbaugh et al, PLOSone, 2015
Event-Related Potentials (ERPs)

- ERPs are brain electrical response to a specific stimulus event.
- The spatial distribution and temporal response across the scalp provides information about the speed and accuracy in processing of sensory stimuli (tones, light, touch).
- Advantages:
  - objective, nonverbal, summative assessment of learning, processing, and attention in awake individuals.
  - no acclimation or training for the task
  - no scalp abrasion or shaving
  - rich literature in infants, children and adults
- On-going collaboration with Dennis Molfese at the University of Nebraska.
Profound Auditory ERP Suppression 6d Post-CCI

Pre TBI

Post TBI
ERP Amplitude and Pairwise Coherence Decreased 6d Post-CCI

Pre TBI

Post TBI
Animal Models - Summary

• Animal models can play an important role in developing and validating human concussion assessments for reproducible single and repeated accelerations

• We have a set of novel, **highly translational objective** metrics:
  • For subtle motor changes that occur with TBI (stationary balance)
  • For changes in processing that occur with TBI (ERP)
  • For changes in sleep/wake activity

• We have an on-going collaborations and preliminary data to measure **serum biomarkers, eye tracking and fNIR** in piglets, which has been used successfully to study effects of TBI

• We are interested in working with clinical groups to develop novel assessments, and validate putative metrics with biomarkers, imaging, and invasive or terminal outcomes.
How to Use Animal Studies to Construct Injury Risk Curves

Mechanical Parameter (i.e. Head Acceleration)

Probability of Injury

- 75% probability of injury
- 50% probability of injury
Scaling Relationships – Does age matter?
Ommaya relationship assumes same geometry, stiffness, and deformation threshold

Ommaya et al 1968
Piglets had a significantly higher density of hemispheric axonal lesions than adult mini-pigs (Smith et al., 2000) experiencing the same load magnitude and direction ($6.5 \pm 1.5$ versus $1.9 \pm 0.7$ injured axons/mm$^2$).

Again, the immature piglet brain appears to be more vulnerable to acute (< 6 hr) traumatic axonal injury than the adult.
Using Animal Studies to Construct Human Concussion Risk Curves

- Lack of fidelity with human injury severity
- Most studies focus on TBI with LOC or pathology
- Lack of testing in multiple ages, species, sexes
- Need data on repeated loads and inter-load intervals
- Few studies address long term outcomes
- Lack of clinical management fidelity
- Limited clinically relevant symptom assessments
- Challenges scaling loads and symptoms from animals to humans
Human Studies

• Goal: to identify “real world” scenarios associated with injury

• Ideal biofidelity

• Challenges:
  ▫ Limited biomechanical details
  ▫ Limited objective injury assessment metrics
  ▫ No measured tissue deformations
Risk Curves – What we think we know...

- Greenwald et al, Neurosurg. 2008
- Pellman et al, Neurosurg 2003
- Schnebel et al., Neurosurg 2007
Risk Curves – Technical Challenges

• How, what, when to measure?
  • HOW: helmets, mouthguards, headbands, patches?
  • WHAT: number, which peak, linear, rotational, resultant?
  • WHEN: practices, games, club sports?

• Sensor accuracy and precision, and role of hair and sweat

• Sample size variation for rare events

• Under-reporting
  • lack inexpensive objective diagnostics
  • statistical compensation strategies
Risk Curves – Effect of Errors

Cumulative effect of three types of error on the concussion risk showing the progressive effect of adding sampling variability, under-reporting, and accounting for sensor error.

Elliott et al, in review
Tolerances are Used to Construct Injury Risk Curves

Probability of Injury

Mechanical Parameter (i.e. Head Acceleration)

75% probability of injury

50% probability of injury
Risk Curves – Philosophical Challenges

• Risk curves are injury specific
  • severe or mild deficits?
  • acute, mid-term or long-term deficits?
  • single events or repeated?
  • inter-injury interval

• Risk curves are age specific
  • where do we start – adults or children?
  • can we scale across ages?

• Risk curves may be sex-specific

• What is an acceptable risk? 10% 50%
Where we are on Identifying Concussion…

• There are no objective markers for concussion diagnosis, prognosis, and recovery. *Evaluation and diagnosis is based primarily on signs and symptoms. Combinations of assessments appear to be better than single metrics. Reliability depends on training of provider, effort of participant, and setting.*

• The brain is more susceptible to injury while it is recovering. *Physical and mental rest – little empirical data for how much and how long. Over 80% recover in a few weeks.*

• Existing management guidelines are based on expert consensus with limited empirical evidence.

• There are no randomized clinical trials testing the effectiveness of psychosocial or pharmacological treatments for youth with post-concussive symptoms and prolonged recovery.
Where we are on Understanding Biomechanics of Concussion

• Normal changes during brain development (5-21 yrs) may influence susceptibility to and prognosis following concussion in youth. **Not clear if young brain is more vulnerable to injury or more adaptable in recovery.**

• Existing studies of head injury biomechanics is primarily in adults and more severe TBI. Linear and rotational head movements are important biomechanical triggers for more severe TBIs with LOC. Responses vary with age, and depend on direction, if there was a previous TBI, and when.

• Data are inadequate to define the direction- and age-related thresholds for linear and rotational acceleration specifically associated with concussions in youth. There is no evidence about the number of head impacts or concussions that are tolerable.
Recommendations

Establish objective, sensitive, and specific metrics and markers of concussion diagnosis, prognosis, and recovery in humans and animals

Fund research on age- and sex-related biomechanical determinants of injury risk for concussion in youth, including how injury thresholds are modified by the number of and time interval between head impacts and concussions.

These data are critical for creating concussion risk curves and informing the development of rules of play, effective protective equipment and equipment safety standards, impact-monitoring systems, and training programs.
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